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Every woman over 50 is recommended to have mammograms to monitor for breast cancer, The goal is to detect breast cancer as early as possible. The problem with the technique are well known and range from the exposure to X-rays, the difficulty of analysis, to patient resistance. Normal human breath contains a complex mixture of volatile organic compounds (VOCs). A number of these VOCs have been identified as candidate markers of various cancers (e.g. formaldehyde in breast cancer). Although breast analysis has been shown to have great potential as a diagnostic tool, most of the compounds of interest are exhaled in picomolar concentrations. Real-time breath analysis for these compounds is not possible with existing technology. Cavity ringdown spectroscopy (CRDS) measurement of the rate of absorption of a sample within a closed optical cavity, rather than the standard measurement of the obsorbed signal strength over a given sample path. It maintains much of the simplicity of classical absorption spectroscopy, but has been demonstrated to provided an increase in sensitivity of up 10,000 times. The objective is to evaluate the potential of CRDS to provided real-time formaldehyde concentrations in exhaled breath for the purpose of the detection of breast cancer.

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Introduction:

Background: Every woman over 50 is recommended to have mammograms to monitor for breast cancer. The goal is to detect breast cancer as early as possible. The problems with the technique are well known and range from the exposure to X-rays, the difficulty of analysis, to patient resistance. Normal human breath contains a complex mixture of several hundred volatile organic compounds (VOCs). A number of these compounds have been identified as candidate markers of various cancers (e.g. formaldehyde in breast cancer). Although breath analysis has been shown to have great potential as a diagnostic tool, most of the compounds of interest are exhaled in picomolar concentrations and may also be highly reactive and volatile. Real-time breath analysis for these compounds is not possible with existing technology. Cavity ringdown spectroscopy (CRDS) is a measurement of the rate of absorption of a sample within a closed optical cavity, rather than the standard measurement of the absorbed signal strength over a given sample path. It maintains much of the simplicity and advantages of classical absorption spectroscopy, but has been demonstrated to provide an increase in sensitivity of up 10,000 times. Utilizing CRDS, real-time breath analysis at picomolar levels required may be possible.

Objective: To evaluate the potential of cavity ringdown spectroscopy to provide real-time measurements of formaldehyde concentration in exhaled breath for the purpose of the detection of breast cancer.

Specific Aims: To determine the sensitivity of cavity ringdown spectroscopy to detect formaldehyde under conditions simulating those present in exhaled breath and evaluate the technique's potential in establishing the validity of biomarkers in exhaled breath.

Study Design: A study will be initiated to evaluate the formaldehyde CRDS spectrum using pulsed dye and diode laser systems. We will adapt analytical UV cavity ringdown spectroscopy techniques we designed and use for the ultratrace measurement of a variety of toxic chemicals (e.g. Hg, Pb, various hydrocarbons, dioxins) for the detection of gas phase formaldehyde. A sample chamber will be developed to simulate the variations in gas flow, humidity, etc., present in exhaled breath. A tunable mid-IR quantum cascade diode laser centered over the formaldehyde absorption at 3550 nm will be used to establish the optimum sensitivity and robustness of the technique under conditions consistent with exhaled breath.

Relevance: The establishment of formaldehyde levels in the breath as a reliable biomarker for breast cancer would significantly improve both testing and detection rates. This could result in a significant impact on the success of treatment, as well as reduce the financial burden of treating breast cancer on the economy as a whole. The proposed research does not aim to achieve all these goals but it could provide the crucial first step along the path, a real-time noninvasive diagnostic "breathanalyzer". Finally, the successful application of CRDS to the detection of formaldehyde in exhaled breath may provide the foundation for many other medical applications using a cavity ringdown-based "breathanalyzer."

Present Status

The statement of work in the original proposal detailed the effort required to design, construct and evaluate a prototype cavity ringdown spectrometer to facilitate breath analysis as a diagnostic tool. The individual tasks to be performed and progress made in each are described below. The core effort focuses on the optimization and evaluation of a laboratory cavity ringdown spectrometer for gas-phase formaldehyde detection.

NOTE: This research grant was awarded late September 2003, following the PI's transfer from Mississippi State University to taking the position of Chair the University of Tulsa. This change in institution has resulted in slower progress than expected. Progress has been hindered by several different factors including

Construction delays with respect to the PI's research laboratory at TU.

The late withdrawal (after initial acceptance) of a postdoctoral associate and the associated delays with finding a replacement. Dr. Li took up the position in May, 2004.

Problems encountered by Alpes Laser Inc., in constructing and delivery of the quantum cascade laser

Requirement to purchase a dye laser system (with university provided funds) to perform the planned UV studies.

As the effect of these delays on the project became evident, a 12 month no-cost extension was requested in June 2004.

Task 1: Breath Analysis CRDS System Development: Design and construct a CRDS system for optimum detection of formaldehyde. This will involve the modification of an existing CRDS system.

A Quantum Cascade Diode laser was ordered in September 2003 with initial delivery scheduled for March 2004. Unfortunately, the initial manufacturing process was unsuccessful. Meanwhile, the remainder of the system components were purchased and assembled. A demonstration QCL laser was requested from, and provided by Alpes Laser. This laser has allowed us to familiarize ourselves with the properties of Quantum Cascade lasers but, as it did not have the required specifications (in terms of both wavelength, or line width), no formaldehyde cavity ringdown measurements could be made. A new delivery date for the specified QC laser was set for the end of September 2004/early October but a specific date for delivery has not been obtained at the time of writing this report.

In the original statement of work it was stated that while we were waiting for the QCL, research would be done in the UV using an existing narrow line width dye laser system. However, in taking up the position of Chair at the University of Tulsa meant that access to the Mississippi State University dye laser system was no longer available. Therefore a narrow line (0.03 cm^{-1}) dye laser (Lambda Physik Scanmate 2E) was purchased (using university-provided funds). This laser was installed shortly after the research laboratory was completed (August 2004). Highly reflective CRDS mirrors

(99.99%) at 340 nm have been purchased from Los Gatos Research. Cavity designed and supporting instrumentation purchased. The UV system is now operational. Final shakedown experiments will be done over the next month to integrate the CRDS setup. Once this is done, experiments to determine detection limits, calibration and appropriate analytical procedures will be undertaken in the UV region.

Following the delivery of the QCL, experiments in the IR will be performed in parallel to those being undertaken in the UV spectral region.

Task 2: Software Modification: Modify an existing LabView software packet to analyze the data and control the diode laser and sampling system.

An undergraduate, Thomas Hodder, is doing his senior research project (in association with the postdoctoral research associate) on modifying an existing labview program to control both the new dye laser system and the QCL. The dye laser system software package is working satisfactorily but it is expected that additional modifications will be implemented as needed.

It is expected that a report summarizing this effort will be submitted as Mr. Hodder's senior thesis.

Task 3: Sampling interface:

A sample system previously used for trace gas analysis has been modified and experiments to validate the system are scheduled to be performed under Task 1.

Task 4: CRDS system optimization: Establish the sensitivity of the technique in terms of detection limits, evaluate the effect of typical interferents and investigate approaches necessary to optimize operation. Compare results obtained using the UV and infrared spectral regions.

We expect to begin performing the formaldehyde CRDS experiments in the UV as soon as Tasks 1 and 3 are completed.

Task 5: Data Dissemination:

Results will be disseminated in both conference presentation and peer-reviewed publications.

KEY RESEARCH ACCOMPLISHMENTS: Due to the delayed start, research is to preliminary to define accomplishments at this point.

REPORTABLE OUTCOMES: None at this time.